

## REMARKS

### **Amendments to the Claims**

Claim 1 is amended to incorporate the phrase “under conditions which allow the reovirus to replicate in ras-activated cells.” Support is provided, for example, in claim 9(b) as filed and in paragraph [0029] (page 5) of the specification as filed. Likewise, claim 23 is amended to incorporate the phrase “under conditions which allow the oncolytic virus to replicate in neoplastic cells” and claims 25 and 28 are amended to incorporate the phrase “under conditions which allow the oncolytic virus to selectively replicate in said neoplastic cells.”

Claim 1 is amended by rewriting the “wherein” clause as a corresponding method step “identifying the sample as comprising ras-activated neoplastic cells if the reovirus can replicate in the cells.” Support is provided generally throughout the application, for example in paragraph [0029] (page 5) of the specification as filed. Likewise, claim 25 is amended by rewriting the “wherein” clause as a corresponding method step.

Claim 16 is amended to insert the phrase “determining the ability of the reovirus to replicate in the cells.” Support is provided, for example, in claim 9(c) as filed and in paragraph [0029] (page 5) of the specification as filed. Likewise, claim 31 is amended to include the phrase “determining the ability of the oncolytic virus to replicate in the cells.”

Claim 23 is amended to incorporate the inadvertently omitted word “a.”

Claims 23, 25, and 28 are amended to include the phrase “provided the oncolytic virus is not an adenovirus” as supported in paragraph [0035] (page 7) of the specification as filed. Respective dependent claims 24, 27 and 30 are likewise amended.

Claim 25 is amended to clarify the language of the phrase “A method of detecting neoplastic cells having a particular phenotype in a biological sample,” by amendment to the wording “A method of detecting neoplastic cells in a biological sample, the neoplastic cells having a particular phenotype.”

Claim 25 has been amended by incorporating the additional element “selected from ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency” from claim 26.

Accordingly, claim 26 has been canceled. Likewise, claim 29 is canceled and its elements are incorporated into claim 28.

No new matter has been introduced. The Examiner is respectfully requested to enter these amendments.

### **Response to Elections/Restrictions**

Applicants gratefully acknowledge withdrawal of the restriction between subgroups iii and iv.

The Examiner states on page 3, lines 5-6 of the Office Action that the restriction requirement is maintained for subgroups i, ii and x-xiv. Subsequently, in lines 11-24, the Examiner rennumbers subgroups x-xiv to viii-xii. Thus, the restriction being maintained appears to be directed to subgroups i, ii, and viii-xii **as renumbered** in the Office Action, while renumbered subgroups iii-vii are not maintained. The Examiner is kindly requested to confirm Applicants' understanding of the renumbered subgroups or provide further clarification.

The Examiner states that claims 1-6, 8-13, 15, 23-26, 28 and 29 are under examination, and claims 7, 14, 16-22, 27, and 30-33 are withdrawn from consideration. The restriction being maintained is respectfully traversed for reasons set forth below.

#### *(1) The Office Action does not list all the claims in each group*

Applicants thank the Examiner for clarifying which claims belong to the restricted groups. However, Applicants note that the Office Action does not indicate to which group or subgroups claim 27 belongs. Applicants respectfully request the Examiner provide a complete listing of each group and subgroup, as well as the claims therein, pursuant to MPEP § 817.

#### *(2) There is no serious examination burden*

If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions (MPEP § 803).

*(2) (a) There is no serious burden to examine Groups I and II together*

A search for Group I, which comprises a step of identifying a neoplasm, will necessarily uncover all art relevant to Group II, which also comprises the **same step** of identifying a neoplasm. Therefore, the restriction of Group II from Group I should be withdrawn because there is no serious burden to search for Group II once Group I has been searched.

*(2) (b) There is no serious burden because the inventions are related*

Applicants previously argued that the restricted groups are related. The Examiner responds that Applicants' argument does not demonstrate that the viruses can be used together, and alleges that the specification does not disclose, for example, using avian reovirus (subgroup ii) in combination with vesicular stomatitis virus (subgroup xii). The Examiner thus concludes the restricted groups are unrelated.

However, the groups are related because the application specifically teaches that they can be used together. Applicants respectfully point the Examiner to paragraph [0038] (page 8):

Another aspect of this invention provides a kit comprising **at least two viruses** which can be used to phenotype tumors according to the present invention. The viruses are preferably selective for neoplasms with different phenotypes. Preferably, the viruses are selected from the group consisting of reovirus, VSV, the ONYX-015 virus, and the Delta24 virus. (Emphasis added)

Thus, the specification clearly teaches that at least two viruses can be used together to phenotype tumors. The viruses which can be used together include those which be used to phenotype tumors according to the present invention (i.e., the viruses in subgroups i-xii, as renumbered). Moreover, both viruses in the Examiner's example are covered in the paragraph, i.e., avian reovirus (reovirus) and vesicular stomatitis virus (VSV). Therefore, the restriction between groups defined by the viruses of the claimed methods should be withdrawn because the groups are related. Applicants request that the restriction between subgroups i-xii (as renumbered) be lifted.

*(2) (c) There is no serious burden because the inventions all employ oncolytic viruses*

The Examiner alleges that examination of the various groups would require different search terms, different cellular receptors, and different infection specificities. As Applicants previously argued in the reply to the restriction requirement, all the viruses in the claims are oncolytic viruses which selectively infect neoplastic cells but not normal cells and can therefore be searched as such without a serious burden. If the Examiner believes there is difficulty in searching all species, Applicants suggest that the Examiner issue a requirement for election of species

#### *Conclusion*

Therefore, the Examiner should withdraw the restriction of claims 7, 14, 27, and 30, and optionally may issue an election of species requirement.

#### **Objections**

Applicants have amended claim 23 to correct the typographical error noted by the Examiner. Withdrawal of this objection is respectfully requested.

#### **Rejections under 35 U.S.C. § 112**

Claims 1-6, 8, 23-26, 28 and 29 stand rejected under 35 U.S.C. § 112 as allegedly being indefinite.

The Examiner states that claims 1, 23, 25, and 28 should include an incubation step. Applicants have amended these claims to include such a step. For example, claim 1 is amended to incorporate the phrase "under conditions which allow the reovirus to replicate in ras-activated cells." Withdrawal of this rejection is respectfully requested.

The Examiner rejects claim 25, alleging that the preamble "[a] method of detecting neoplastic cells having a particular phenotype in a biological sample" is unclear. Applicants have amended claim 25 to recite "[a] method of detecting neoplastic cells in a biological sample, the neoplastic cells having a particular phenotype selected from ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency."

The Examiner rejects claims 25 and 28, alleging that the phrase "a particular phenotype" is unclear because it is unclear what type of biological properties this language refers to. The Examiner also alleges that the specification fails to provide the meaning of "a particular phenotype." Applicants respectfully point the Examiner to paragraph [0061] (page 13) of the specification as filed:

"Phenotyping" a tumor means classifying a tumor according to its phenotype. For example, tumor phenotypes include ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency. The phenotypes are not mutually exclusive, namely, a tumor may be phenotyped into more than one class.

Although the phrase is clear, Applicants have amended claims 25 and 28 to specify that the particular phenotype is selected from ras pathway activation, interferon-resistance, p53-deficiency and Rb-deficiency, as described in the respective dependent claims 26 and 29.

In view of the preceding, withdrawal of the corresponding rejections under 35 U.S.C. § 112 is respectfully requested.

#### **Rejection of Claims 1, 2, 4-6, 25, and 26 Under 35 U.S.C. § 102(b) over Strong**

The Examiner rejects claims 1, 2, 4-6, 25, and 26 under 35 U.S.C. § 102(b) as allegedly anticipated by Strong (Strong, J.E. et al., EMBO (1998) Vol. 17, No. 12, 3351-3362). The Examiner states that the phrase in claims 1, 2, and 4-6 "wherein the ability of the reovirus to replicate..." allegedly recites a property that is inherent to cells that support reovirus replication, thus the claims lack a resolution step wherein the observation of reovirus replication is used to identify the presence of a neoplasm. Also, the Examiner rejects claims 25 and 26 over the corresponding "wherein" phrase in claim 25.

For similar reasons, the Examiner rejects claims 1-6, 25, and 26 as allegedly anticipated by Norman (Norman, K.L. et al., J. Clin. Invest. (April 2000) Vol. 105, No. 8, 1035-1038); claims 1-6, 8, 25, and 26 as allegedly anticipated by Coffey (Coffey, M.C., et al., Science (November 1998) Vol. 282, 1332-1334); and claims 1-6, 8, 25, and 26 as allegedly anticipated by Hirasawa (Hirasawa, K., et al., Cancer Res. (March 2002) Vol. 622, 1696-1701).

Applicants have amended claim 1 to recite the step of "identifying the sample as comprising ras-activated neoplastic cells if the reovirus can replicate in the sample." Claim 25 is likewise amended. Because none of these references perform a step of identifying a sample as comprising ras-activated neoplastic cells if the reovirus can replicate in the cells, none of the cited references anticipate the instant claims. Withdrawal of the corresponding rejections is respectfully requested.

**Rejection of Claims 23, 25, 26, 28, and 29 under 35 U.S.C. § 102(e) over Fueyo**

The Examiner rejects claims 23, 25, 26, 28, and 29 under 35 U.S.C. § 102(e) as allegedly being anticipated by Fueyo (U.S. Pat. Appl. No. 2004/0029112).

The methods disclosed in Fueyo employ adenovirus. Applicants have canceled claims 26 and 29, and have amended claims 23, 25, and 28 to recite "provided the oncolytic virus is not an adenovirus." Corresponding amendments have also been made in the respective dependent claims. Therefore, Fueyo does not teach each and every element of the claimed invention, and withdrawal of this rejection is respectfully requested.

**Rejection of Claims 9-13 and 15 under 35 U.S.C. § 103(a) over Fueyo and Norman**

The Examiner rejects claims 9-13 and 15 under 35 U.S.C. § 103(a) as being unpatentable over Fueyo in view of Norman.

Claim 9 is directed to a method of diagnosing a ras-activated neoplasm in an animal, comprising providing a biological sample from the animal, wherein the sample comprises cells; contacting the sample with a reovirus under conditions which allow the reovirus to replicate in ras-activated cells; determining the ability of the reovirus to replicate in the sample; and identifying the animal as having a ras-activated neoplasm if the reovirus can replicate in the sample.

Norman teaches a method of inducing cancer in severe combined immunodeficient mice by implanting *v-erbB*-transformed NIH-3T3 fibroblast cells, and injecting the resulting tumors with reovirus. Norman also teaches testing reovirus on a variety of cancer cell lines in vitro.

Fueyo teaches a method of treating cancer in animals using a mutant adenovirus that is targeted to cells with a mutant retinoblastoma pathway, wherein the animals are treated without harming cells with a wild type retinoblastoma pathway.

The Examiner states that "in light of Norman, one skilled in the art would appreciate that Fueyo's methods could be practiced with reovirus." However, this contradicts the Examiner's own restriction requirement. "In a national application containing claims directed to more than a reasonable number of species, the examiner should not require restriction to a reasonable number of species unless he or she is satisfied that he or she would be prepared to allow claims to each of the claimed species over the parent case, if presented in a divisional application filed according to the requirement" (MPEP, § 806.04(h)). By issuing the restriction requirement, the Examiner must be satisfied that claims to reovirus and adenovirus would be allowable (i.e., novel and **unobvious**) over each other. Consequently, it is improper and contradictory for the Examiner to make an obviousness rejection by combining references (Fueyo and Norman) separately directed to species (adenovirus and reovirus) that the Examiner has **already** determined to be mutually nonobvious.

Also, "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)" (MPEP, §2143.01). The rejection is improper because the Examiner has not shown a suggestion in the cited references of the desirability of their combination.

Moreover, Fueyo does not teach or suggest the claimed methods of diagnosing a ras-activated neoplasm in an animal. For example, Fueyo does not teach or suggest a step of providing a biological sample from the animal contacting the biological sample with a reovirus. Norman does not remedy these deficiencies.

For the preceding reasons, the claimed invention is not obvious in view of the cited references, and withdrawal of this rejection is respectfully requested.

**Rejection of Claims 8-13, 15 and 24 under 35 U.S.C. § 103(a) over Fueyo and Strong**

The Examiner rejects claims 8-13, 15 and 24 under 35 U.S.C. § 103(a) as being unpatentable over Fueyo in view of Strong.

The Examiner states that "it would have been obvious to modify Fueyo with Strong teachings." However, as noted above with respect to Fueyo and Norman, this defies the Examiner's own restriction requirement. As above, it is improper and contradictory for the Examiner to make an obviousness rejection by combining references (Fueyo and Strong) separately directed to species (adenovirus and reovirus) that the Examiner has **already** determined to be mutually nonobvious.

Also, as noted above with respect to Fueyo and Norman, the rejection is improper because the Examiner has not shown a suggestion in either Fueyo or Strong of the desirability of their combination.

Further, as noted above, the methods disclosed in Fueyo do not teach or suggest essential elements of claims 9-13. Moreover, Fueyo does not teach or suggest the use of viruses other than adenovirus, and thus does not teach the reoviruses, vaccinia viruses mutated in the K3L and/or E3L region, parapoxvirus orf viruses mutated in the OV20.0L gene, influenza viruses mutated in the NS-1 gene, herpes viruses mutated in the  $\gamma$ 134.5 gene, or vesicular stomatitis virus as required by claim 24.

Strong does not remedy these deficiencies. Strong teaches the creation of artificial ras activated NIH 3T3 fibroblasts in culture. By contrast, the claimed invention is to a method of diagnosing a ras-activated neoplasm **in an animal** which requires providing a biological sample **from the animal**, and determining the ability of the reovirus to replicate in the sample. Moreover, Strong does not teach or suggest a step of identifying ras-activated neoplasm because Strong **already knows** the identity of the artificially created ras activated NIH 3T3 fibroblasts by virtue of having designed and created them.

For the preceding reasons, withdrawal of this rejection is respectfully requested.

Applicant : Bradley G. Thompson, et al.  
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## Conclusion

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.


In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5078.

Enclosed is a \$60 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06 1050.

Respectfully submitted,

Date:

September 30, 2005

  
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